II. REMARKS

Formal Matters

Claims 1-9, 15, and 17-19 are pending after entry of the amendments set forth herein.

Claims 1-9, 15, and 17-19 were examined and were rejected.

Claim 1 is amended. Support for the amendment to claim 1 is found in throughout the specification, including, e.g., at paragraph 0026. As such, no new matter is added by the amendment to claim 1.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Examiner Interview

The undersigned Applicants' representative thanks Examiner David Venci and Examiner Long Le for the courtesy of a telephonic interview which took place on January 12, 2007, and which was attended by Examiner Venci, Examiner Le, inventor Ken Y. Lin, and Applicants' representative and Paula A. Borden.

During the interview, the rejection of claims 1-9, 15, and 17-19 under 35 U.S.C.§ 112, first paragraph, was discussed.

Rejection under 35 USC §112, first paragraph

Claims 1-9, 15 and 17-19 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement.

The Office Action stated that: 1) Applicants' specification does not describe the exact experimental conditions for performing the claimed two-step method, comprising modifying SDMA and arginine, followed by detecting ADMA in the sample; 2) Applicants' specification does not describe the exact reaction conditions for reacting a sample with an α-dicarbonyl compound, resulting in detectable ADMA; 3) Applicants' specification does not describe a detecting means capable of detecting ADMA in the product of a reaction between a sample and an α-dicarbonyl compound; and 4) other than phenylglyoxal derivatives, Applicant's specification does not contemplate any other modified SDMA derivatives or modified arginine derivatives. Applicants respectfully traverse the rejection.

As discussed during the telephone interview, detection of ADMA levels in a sample, e.g., a biological sample, has clinical importance, as elevated ADMA levels are associated with various disorders. Specification, paragraph 0004. Current methods of detecting ADMA suffer from low efficiency and sensitivity, primarily due to the difficulty in distinguishing ADMA from SDMA and from arginine. This is because ADMA, SDMA, and arginine are chemically similar. Specification, paragraph 0027. The instant application describes a method that involves a reaction that modifies SDMA and arginine, but not ADMA. Specification, paragraph 0028; and paragraphs 0097-0099. A sample that includes SDMA and/or arginine in addition to ADMA is modified according to the claimed methods. The modification reaction results in a sample that includes modified SDMA and/or modified arginine, and ADMA. The ADMA is distinguishable from the modified SDMA and/or modified arginine in the sample. ADMA is readily detectable, using any method, including known methods. Standard methods of detecting ADMA include, e.g., HPLC, capillary electrophoresis, and the like, as described in the specification. Specification, paragraphs 0043-0067.

The specification provides ample description of the claimed method.

The Office Action stated that the specification does not describe the exact experimental conditions for performing the claimed two-step method, comprising modifying SDMA and arginine, followed by detecting ADMA in the sample. However, the instant specification provides ample description of experimental conditions for performing the claimed method, involving contacting a sample with an α-dicarbonyl compound, to produce modified ADMA and modified arginine, and detecting ADMA.

- The specification provides a list of suitable α-dicarbonyl compounds in paragraphs 0030 and 0031.
- The specification describes suitable concentrations of the α-dicarbonyl compound. Specification, paragraph 0034.
- The specification provides reaction times and temperatures for the reaction between the α-dicarbonyl compound and the SDMA and/or arginine. Specification, paragraphs 0035 and 0038.
- Exemplary reaction conditions are also described. Specification, paragraph 0099.

Thus, given the guidance in the specification, those skilled in the art could readily carry out a method as claimed.

The specification provides ample description of methods for detecting ADMA.

The Office Action stated that the specification does not describe a detecting means capable of detecting ADMA. As discussed during the telephone interview, the specification describes **at least four** methods of detecting ADMA. Specification, paragraphs 0043-0067. These methods include HPLC, capillary electrophoresis, immunoassays, and liquid chromatography-tandem mass spectrometry.

- **HPLC** As discussed in the specification, HPLC methods for detecting ADMA were known in the art. Specification, paragraph 0044. The instant specification provides a detailed description of an exemplary method of using HPLC to detect ADMA in a sample. Specification, paragraphs 0045-0050. See, e.g., Teerlink et al. (2002) *Anal. Biochem.* 303:131-137; Dobashi et al. (2002) *Analyst* 127:54-59; Pi et al. (2000) *J. Chromatogr. B. Biomed. Sci. Appl.* 742:199-203; Chen et al. (1997) *J. Chromatogr. B. Biomed. Sci. Appl.* 692:467-471; Anderstam et al. (1997) *J. Am. Soc. Nephrol.* 8:1487-1442; and Pettersson et al. (1997) *J. Chromatogr. B. Biomed. Sci. Appl.* 692:257-262.
- **Capillary electrophoresis** As discussed in the specification, capillary electrophoresis methods of detecting ADMA were known in the art. Specification, paragraphs 0052-0053. See, e.g., Causse et al. (2000) *J. Chromatogr. B. Biomed. Sci. Appl.* 741:77.
- **Immunoassays** As described in the instant specification, immunoassays can be designed that take advantage of the ability to distinguish modified SDMA and modified arginine from ADMA. Specification, paragraphs 0054-0065. Design and execution of such immunoassays is well within the skill level of those in the art.
- **Liquid chromatography-tandem mass spectrometry** As discussed in the specification, liquid chromatography-tandem mass spectrometry methods of detecting ADMA were known in the art. Specification, paragraph 0066. See, e.g., Vishwanathan et al. (2000) *J. Chromatogr. B. Biomed. Sci. Appl.* 748:157-166.

The specification contemplates use of any of a variety of α-dicarbonyl compounds.

The Office Action stated that, other than phenylglyoxal derivatives, Applicant's specification does not contemplate any other modified SDMA derivatives or modified arginine derivatives. This is not correct. As noted above, the specification provides a list of suitable α-dicarbonyl compounds in

paragraphs 0030 and 0031. Phenylglyoxal is but one example of a suitable α-dicarbonyl compound that can be used.

The instant specification provides reaction conditions for carrying out the modification step such that the skilled person could easily carry out such a modification reaction; and the instant specification provides ample description of various methods for detecting ADMA. As such, those skilled in the art, given the guidance in the specification and the knowledge available in the art, could readily carry out the instant method as claimed.

The cited art does not support a conclusion of lack of enablement of the instant claims.

The Office Action asserted that the state of the prior art appears to recognize a high degree of unpredictability in the field of arginine derivatization. In support of this assertion, the Office Action cited the following art: 1) Baburaj et al. ((1994) *Biochim. Biophys. Acta* 1199:253; "Baburaj"); 2) Schwarzenbolz et al. ((1997) *Z. Lebensm. Unters. Forsch. A* 205:121-124; "Schwarzenbolz"); and Sopio and Lederer ((1995) *Z. Lebensm. Unters. Forsch.* 201:381-386; "Sopio").

Baburaj

Baburaj discusses two α-dicarbonyl compounds, designated HOCGO and DMACGO. The Office Action stated that Baburaj found the HOCGO and DMACGO are capable of reacting with cysteine and lysine residues. However, as discussed during the telephone interview, the possibility that HOCGO and DMACGO might be capable of reacting with cysteine and lysine residues has no bearing on a determination of whether the instant claims are enabled. **All that is required is that the α-dicarbonyl compound modify any SDMA and any arginine that may be present in the sample.** The possibility that an α-dicarbonyl compound might modify a cysteine or a lysine residue is irrelevant. Any side reactions that would modify cysteines or lysines would not be expected to adversely affect modification step (a) or detection step (b). As such, Baburaj does not lead to a conclusion of lack of enablement.

Schwarzenbolz

Schwarzenbolz discusses reaction of glyoxal with proteins. The Office Action stated that Schwarzenbolz teaches that under certain conditions, glyoxal produces two arginine derivatives.

However, many chemical reactions will produce, in addition to a main product, one or more side products. The side products discussed in Schwarzenbolz are minor. Any side products that may be produced in such low quantities would not be expected to adversely affect modification step (a) or detection step (b). As such, Schwarzenbolz does not lead to a conclusion of lack of enablement.

Sopio

Sopio discusses reaction of 3-deoxypentosulose with *N*-methyl- and *N,N*-dimethylguanidine as model reagents for protein-bound arginine and for creatine.

The Office Action stated that under certain experimental conditions, deoxyosones result in two tautomeric products; and stated that it is not clear whether these and other derivatives are contemplated, and whether such derivatives are distinguishable from ADMA.

However, many chemical reactions will produce, in addition to a main product, one or more side products. The side products discussed in Sopio are minor. Any side products that may be produced in such low quantities would not be expected to adversely affect modification step (a) or detection step (b). As such, Sopio does not lead to a conclusion of lack of enablement.

Conclusion as to the rejection under 35 U.S.C.§112, first paragraph

Applicants submit that the rejection of claims 1-9, 15 and 17-19 under 35 U.S.C. §112, first paragraph, have been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 USC §112, second paragraph

Claims 1-9, 15 and 17-19 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

The Office Action stated that the phrase "said sample comprises ADMA and at least one of SDMA and arginine" is inconsistent with the preamble phrase "a sample comprising ADMA, SDMA, and arginine."

Claim 1 is amended to recite "a sample comprising ADMA and at least one of SDMA and arginine" in the preamble.

The Office Action stated that the recitation "said modified SDMA and said modified arginine are distinguishable" is indefinite. The Office Action stated that the "identity of object(s) and/or step(s), if any, required for performing distinguishing is not clear." Office Action, page 6. Applicants respectfully traverse the rejection.

Claim 1 recites, in step (a), "wherein said modified SDMA and said modified arginine are distinguishable from ADMA." Step (a) recites reacting any SDMA or arginine that may be present in the sample with an α-dicarbonyl compound, resulting in modified SDMA and modified arginine, which, as discussed in the specification, are distinguishable from ADMA. The meaning of the phrase ""wherein said modified SDMA and said modified arginine are distinguishable from ADMA" would be clear to those skilled in the art. As such, claim 1 need not be amended.

Applicants submit that the rejection of claims 1-9, 15 and 17-19 under 35 U.S.C. §112, second paragraph have been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-276.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Jan. 18, 2007

By: _____
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